REMARKS

Claims 1-36 are pending in the present application. Claims 1-22, 30 and 31 were withdrawn by the Examiner after restriction, leaving claims 23-29 and 32-35 under consideration. Applicants have amended claims 23, 26, and 32. Support for these amendments can be found throughout the application as filed, e.g., at page 1, line 10 (full name of Wnt5a as added to claim 1), page 8, lines 7-10 (amendment to claim 26), page 41, lines 29-30 (amendments to claim 23) and the claims as filed, e.g., claims 1 (full name of Wnt5a) and 32 (administration of a cell), *inter alia*. In addition, new claims 33-36 have been added; support for these new claims can be found throughout the application as filed, e.g., at page 8, lines 4-7; page 9, lines 1-4; page 6, lines 1-3; and page 41, lines 29-30, *inter alia*.

No new matter has been added.

Interview Summary

As a first matter, applicants' undersigned representative wishes to thank Examiner Sgagias and Examiner Crouch for the courtesy of the telephone conversation on June 20, 2006, in which the written description and enablement rejections were discussed. As the Examiner noted in the Interview Summary mailed June 23, 2006, it was agreed that applicants would delete the reference to a biologically active fragment or mutant thereof in claim 23 to overcome the written description rejection. The enablement rejection was also briefly discussed, but no agreement was reached on that issue.

Claim Objections

Claims 23-29 and 32 were objected to for informalities.

Claims 23-29 were objected to for reading on a non-elected invention. While applicants maintain that the restriction is improper, applicants have amended claim 23 to remove the language "or who is at risk of developing."

Applicants further note that in the restriction requirement mailed on October 19, 2005, the Examiner stated that claim 23 was generic to two species of nucleic acid administration. Applicants selected the species of Claim 23 wherein the nucleic acid is administered to the

subject by removing a cell from the subject and transducing the cell with a nucleic acid molecule and returning the cell to the subject. Applicants have amended claim 23 to limit it to the selected species, but reserve the right to pursue the unselected species at a later date or in a later application.

In addition, claim 23 was rejected to for the use of the abbreviation "Wnt5a." Applicants have amended claim 23 to set forth the full name of the Wnt5a gene.

Applicants submit that these amendments correct the informalities, and request withdrawal of the objections.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph – Written Description

At pages 3-5 of the Office Action, claims 23-29 and 32 were rejected as allegedly failing to comply with the written description requirement. At page 4, the Office Action states:

> When the claims are analyzed in light of the specification, instant invention encompasses a polynucleotide sequence corresponding to a Wnt5a biologically active fragment or mutant thereof. ... the specification discloses the use of wild type Wnt5a which has been isolated from human or mouse, however, there is no description as to what would have been the complete structure for the sequence of Wnt5a biologically active fragment or mutant thereof isolated from any mammalian or nonmammalian species and how it is related.
>
> ... the only characteristics described is function that the fragment/mutant will treat a subject who has Wnt5a-associated hematopoietic cancer but since all the species will have all that characteristic such cannot be used to distinguish one from the other. Applicant's specification does not teach what are the characteristics of polynucleotide sequences from any mammalian and non-mammalian species except for the wild type human or mouse Wnt5a.
>
> In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that applicant is in possession of the genus of wnt5a nucleic acid molecules, including fragments and mutants thereof other than human and mouse at the time of application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

As discussed in the telephone interview on June 20, 2006, applicants have amended claim 23 to remove the phrase "or a biologically active fragment or mutant thereof," which Examiners

Crouch and Sgagias agreed would overcome the rejection for lack of written description; see the Examiner's Interview Summary, mailed June 23, 2006.

For at least these reasons, applicants submit that the claims as amended have ample support in the application as filed, and request withdrawal of the rejection of claims 23-29 and 32 under 35 U.S.C. § 112, first paragraph.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph – Enablement

Claims 23-29 and 32 were rejected at pages 5-12 of the Office Action as allegedly lacking enablement.

Claim 23 recites a method of treating a subject who has wingless-related MMTV integration site 5a (Wnt5a)-associated hematopoietic cancer, the method comprising administering to the subject a blood cell transduced with a nucleic acid molecule comprising a sequence that encodes Wnt5a, and, optionally, a sequence that encodes a detectable marker, wherein the amount of the nucleic acid molecule delivered is sufficient to generate a therapeutically effective amount of Wnt5a.

Claim 32 further defines the method recited in claim 23 by specifying that the administering step includes removing a blood cell from the subject; transducing the cell with a nucleic acid molecule comprising a sequence that encodes Wnt5a, and, optionally, a sequence that encodes a detectable marker; optionally culturing the cell; and returning the cell to the subject.

At page 8, the Office Action states:

> While the specification provides extensive teachings pertaining to Wnt5a protein expression, in vitro or in vivo (specification p 32-37), the specification fails to provide any relevant teachings or specific guidance or working examples with regard to transducing a cell ex vivo with wnt5a and/or obtaining any cells from a subject, transduce cells ex vivo with wnt5a or a biologically active fragment or mutant thereof, reintroduce the cells into the subject wherein therapeutic levels of the transgene are produced to treat a subject with Wnt5a hematopoietic cancer, particularly AML. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for treating cell based Wnt5a associated hematopoietic cancer and particularly AML. It would have required

> undue experimentation to make and use the claimed invention without a reasonable expectation of success.

It is axiomatic that what is well known in the art need not be set forth in detail. Methods for making viral vectors suitable for expressing Wnt5a in blood cells were known in the art at the time of filing the application. For example, one of skill in the art would understand that the viral vectors, e.g., retroviral vectors, discussed for use in *in vivo* gene therapy methods would also be suitable for use in transducing cells *ex vivo*. In addition, the Examples describe methods for expressing Wnt5a in a B cell line using a viral vector, see page 49, line 22 to page 50, line 7. Applicants submit that the specification and the level of skill in the art provide ample enablement for methods for expressing Wnt5a *ex vivo*.

Further, the Office Action at page 9 cites Gage, Nature 392:18-24 (1998)[1] for the proposition that cell-based gene therapy is an unpredictable art.

> ...Cage, (Nature, 392: 18-24, 1998) teach that although the hematopoietic field is the most advanced in clinical applications of cell therapy, the number of cells needed to perform the desired function is a limiting variable, and thus the ability to multiply a population of cells may be critical (p 20, 2nd column). The author further noted that difficulties arise as if the cells either cannot self-renew in vitro, as in the heamatopoietic system (p 20, 2nd column). Cage, also describes that although, the use of allogeneic obviates the time and source restrictions inherent in the use of autologous cells, many of the problems associated with the variability and replicative capacity remain (p 21 1st column).

Applicants submit that while Gage notes that there are some difficulties associated with cell based gene therapy in general, these issues are not necessarily applicable to the claimed methods. Gage notes that as few as 3.5×10^3 stem cells would be sufficient to fully reconstitute the hematopoietic system (page 19, col. 1). Therefore, even if expansion *in vitro* is difficult, large numbers of cells are not necessary for the methods to be successful, and the ability to multiply a population of the cells is not critical, contrary to the statement at page 9 of the Office Action. In addition, because Wnt5a is a secreted protein, the cell type that is used is less critical; any blood

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[1] Applicants note that this reference is referred to as "Cage" in the Office Action and Form PTO-892, but is authored by Fred H. Gage. Applicants assume this is merely a typographical error, and request clarification if that is not the case. Further, applicants note that page 19 was missing from the copy attached to the Office Action. Applicants request issuance of a corrected Form PTO-892 and placement of a complete copy of the reference in the file.

cell can be used, as Wnt5a secreted into the circulation would be expected to contact the malignant cells and exert a therapeutic effect.

The Office Action at page 9 further states:

> In addition, when considering the functional requirements of a cell and the limitations imposed by the source of the cell, it becomes clear that there is no single universal donor cell that will be useful for all diseases (Cage, p 23 1st column).

Applicants submit that this statement is not applicable to the present claims, as the claims recite the use of blood cells transduced with Wnt5a (not "any cell") to treat Wnt5a-associated hematopoietic cancer (not "any disease"). Therefore, the availability, or lack thereof, of a "single universal donor cell," is not relevant.

The Office Action states at pages 9-10:

> The specification, failed to guidance and/or working examples with respect to cell targeting, route of administration of transduced cells, dose of transduced cells and levels of gene expression in vivo necessary to treat a subject with a Wnt5a associated hematopoietic cancer. ... The specification however, has not provided any specific guidance or teachings with regard to recombinant cell based methods of Wnt5a or a biologically active fragment or mutant thereof, gene therapy and as to what doses and modes of administering a recombinant therapeutic cell population encompassed by the claims. Kohn et al, (J Intern Med, 249(4): 379-90, 2001) noted that inefficient gene transfer to human hematopoietic stem cells has imposed the major limitation to successful application of gene therapy (p 379, abstract). While progress has been made in recent years for gene transfer in vivo, AML cell based therapy in vivo continues to be unpredictable and inefficient as supported by numerous teachings available in the art.

Applicants respectfully traverse.

It was routine in the art at the time of filing of the present application to isolate blood cells from a subject, and methods were known for transducing those cells, see, e.g., Schmidt-Wolf and Schmidt-Wolf, Clin. Exp. Med 3:4-14 (2003) (copy submitted previously), which is cited at page 42, lines 3-10, of the application as filed. Schmidt-Wolf and Schmidt-Wolf review methods for treating hematopoietic malignancies using genetically modified stem cells, see page 5, 2nd col.

Cavazzano-Calvo et al., Science 288:669-672 (2000), also cited at page 42, lines 3-10, of the application as filed, describes successful treatment of human subjects with severe combined immunodeficiency (SCID)-X1 disease by administering autologous blood cells transduced with a transgene that encodes a missing cytokine receptor. Long term expression of the transgene and clinical improvement was seen in all of the treated subjects. Bai et al., Gene Therapy 10:1446-1457 (2003), also cited at page 42, lines 3-10 of the application as filed, describes the use of a lentiviral vector for stable transduction and transgene expression in human blood cells with high efficiency. In particular, at page 1451-1452, Bai et al. describe achieving transduction efficiencies of as high as 96% in CD34+ hematopoietic stem cells. All three references were incorporated by reference in the present application, see page 9, lines 7-8 of the application as filed, and copies were previously submitted.

In addition, Wnt5a proteins had been successfully expressed in a number of cell types, including the mesodermal stem cell line QCE6 (Brandon et al., Blood 96(13) 4132-4141 (2000)), and fetal liver hematopoietic stem cells (Austin et al., Blood 89(10):3624-3635 (1997)). A copy of the Brandon et al. reference is included with the attached Information Disclosure Statement; the Austin reference was submitted previously.

Thus, methods for transducing blood cells and expressing exogenous genes, e.g., Wnt5a, were described in the present application and known in the art.

It is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. See MPEP 2164.01(c). Applicants note that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); MPEP 2164.01.

Because individuals with normal levels of Wnt5a do not generally have hematological malignancies (see, e.g., Example 10 and Fig. 16), it would be logical to assume that levels of

Wnt5a that are present in a normal subject are sufficient to suppress hematological malignancies, therefore, levels approximating normal would be expected to be therapeutic.

In addition, Figure 15A is a blot that illustrates reduced Wnt5a mRNA levels in subjects with ALL and AML; levels above those would also be expected to be therapeutic. Given this information, one of skill in the art would readily be able to determine a therapeutic dosage without any more experimentation than is routine in the art.

The present specification, at page 36, line 17, to page 37, line 3, also discusses exemplary methods in which an isolated Wnt5a gene is operably linked to a promoter, e.g., an inducible promoter (e.g., a steroid hormone receptor-regulated promoter) and introduced into a human or nonhuman (e.g., porcine) cell and then into a subject. When a steroid hormone receptor-regulated promoter is used, protein production can be regulated in the subject by administering a steroid hormone to the subject. In some embodiments, when the cell is returned to the subject, the cell expresses a statistically normal amount of Wnt5a. Determining how much Wnt5a is normally expressed is routine in the art.

One of skill in the art in the art would appreciate that the disclosures of the present application in combination with the level of skill in the art is more than sufficient to provide guidance for determining doses and routes of administration. Such experimentation would be no more than is normal and routine in the art.

Furthermore, Gage states that hematopoietic cell transplantation "is effective as a treatment for selected high-risk patients with haematological malignancies" (see page 19, 2nd col.), indicating that methods for transplanting cells were well known in the art. Thus, every element of the method is amply enabled by the guidance present in the application as filed or in the state of the art, and non-specific concerns regarding cell therapy are insufficient to raise doubt regarding the enablement of the claimed methods.

For at least the above reasons, applicants submit that the claims as amended are enabled.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 26 was rejected as allegedly being vague and indefinite because it recites the phrase "in connection with a liposome." Applicants submit that this phrase is clear as to what the term "connection" means in relation to the use of liposomes as delivery vehicles, but have amended the claim to recite "by way of a liposome," by which one of skill in the art would understand that the nucleic acid molecules are delivered to the cell using liposomes as a delivery vehicle, see, e.g., page 21, lines 12-24 and page 8, lines 7-10. Applicants submit that the claim as amended is clear and request withdrawal of the rejection under 35 U.S.C. § 112, 2nd paragraph.

Conclusion

Applicants submit that the claims as amended are patentable, and request rapid notification thereof. If the Examiner believes that it would advance prosecution of this application, she is invited to telephone the undersigned attorney at (617) 956-5985.

A check for the Petition for Extension of Time fee is enclosed. A check in the amount of $100.00 is enclosed for the excess claims fee. Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket no. 07917-178001.

Respectfully submitted,

Date: 7/12/2006

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